Protein Crystal Contacts

by Eric Martz, April 2001.
A resource within Protein Explorer

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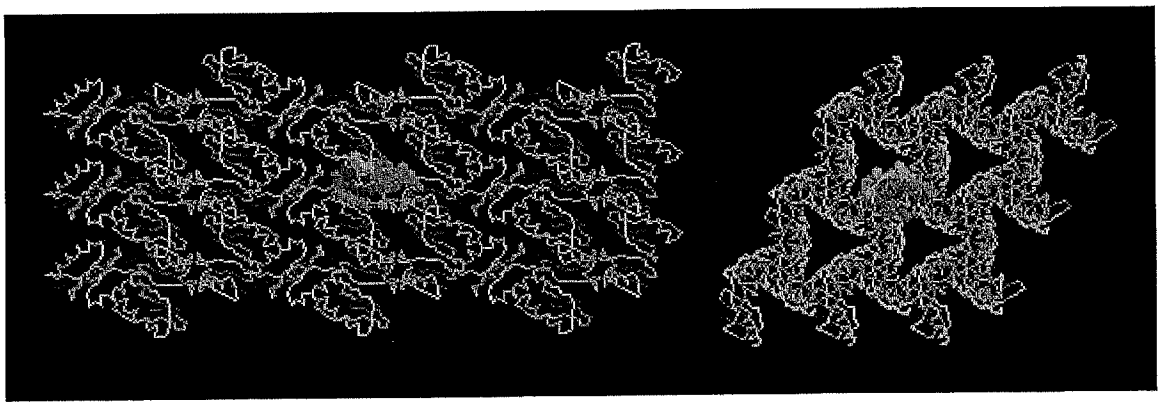
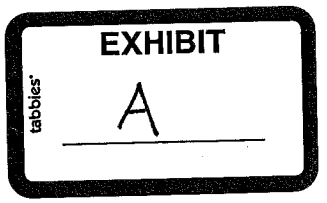
The term **crystal contacts** means interchain or intermolecular contacts that occur solely as the result of protein crystallization (2). These are distinguished from **specific protein complexes** (such as an antibody complexed to a protein antigen) or **oligomer interfaces** (such as in the tetramer of hemoglobin), which occur with the uncrystallized proteins. The term **specific interfaces** can be used to embrace both of these categories. Both specific interfaces and crystal contacts typically occur in crystals, but only the latter are artifacts of crystallization. For more about oligomers, and their structures, see Probable Quaternary Structures.



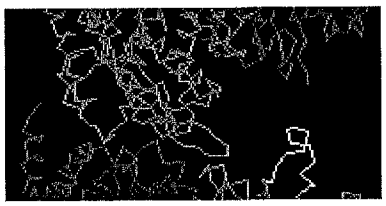
Crystal of 1PGB from two orthogonal views.
Central asymmetric unit spacefilled.

Conformation May Be Altered by Crystal Contacts

Crystal contacts may influence the conformation of a protein. A likely example occurs in the crystal of malate dehydrogenase for 4MDH. Malate dehydrogenase is normally a homodimer. This can be confirmed by consulting Probable Quaternary Structures for 4MDH. (There is a link to Probable Quaternary Structures in the External Resources Window accessed from PE's Site Map. Use the link to PQS to check the PQS report for your molecule.)



In 4MDH, each chain in the homodimer experiences different crystal contacts. Chain A has crystal contacts near the catalytic site, absent for chain B. These crystal contacts **influence the**



4MDH Crystal

conformation of residues 93-99. To visualize this in Chime, see Crystal Contacts in Malate Dehydrogenase. (Thanks to Gale Rhodes for this example.)

Alignment of homodimer chains in 4MDH shows differing conformations of 93-99 (stereo).

The asymmetric unit in 4MDH (contained in the published PDB file available from the Protein Data Bank) contains one homodimer. The crystallographic unit cell contains 4 homodimers. The above-linked Chime presentation on 4MDH displays three adjacent crystallographic unit cells generated with DeepView (figure at left). In all three figures above, residues 93-99 are colored red or yellow. The yellow loops are surrounded by solvent, while the red loops contact another chain in the crystal. This contact appears to be responsible for the different conformations of the loops.

It is also possible that a protein can have two different conformations in two different crystals, resulting from the occurrence of differing crystal contacts in each case. (A good example of this would be welcome.)

Characteristics of Crystal Contacts vs. Specific Interfaces

Dasgupta *et al.* (2) studied 58 oligomers and 223 nonvirus crystals with good resolution and completeness. They found that "crystal contact patches are frequently **smaller** than patches involved in oligomer interfaces". Contact patches of 10 to 100 atoms were common at crystal contacts. Patches involving 100-1,000 atoms were common in oligomer interfaces but rarely seen in crystal contacts. Nevertheless, the total number of atoms involved in crystal contacts vs. oligomer interfaces were about the same; that is, the larger number of small crystal contact patches involved about the same number of atoms as the smaller number of large oligomer interfaces. They also observed that crystal contacts tend to involve more **polar** interactions, while nonpolar interactions tend to predominate in oligomer interfaces. "Hydrophobic interactions lead to disordered precipitates, and not to crystals."

Visualizing Crystal Contacts in Protein Explorer

Published PDB files never show all of the crystal contacts occurring on each chain. It is a good idea to look at all contacts for each chain to get an idea where they might be affecting the conformation. Unfortunately, there is presently no server that generates a PDB file ready for inspection of crystal contacts in Protein Explorer.

Here are some examples of PDB files showing crystal contacts. These files were constructed using the DeepView/RasMol method described below. Each is divided into two models delimited as "NMR"

models. Model 1 is the original aysmmetric unit, and model 2 contains all crystal contact atoms within 5 Å.

To view the 5 Å shell examples below:

1. Go to QuickViews.
2. SELECT All (which selects only model 1).
3. DISPLAY Contacts. **Click OK when asked whether you wish to display crystal contacts.**
4. Use the options in the middle frame to achieve different views.

Example PDB files including a 5 Å shell of crystal contacts:

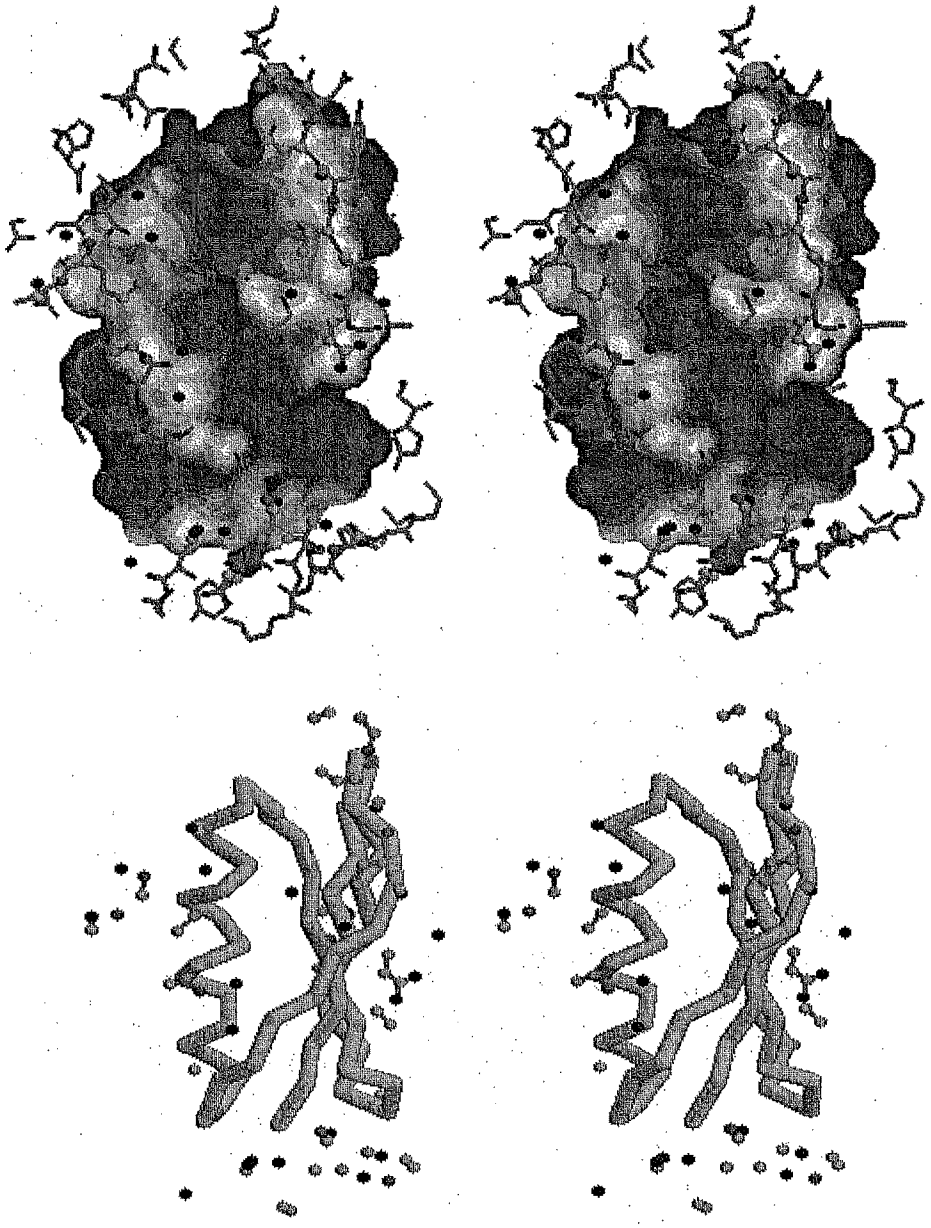
- **1pgb**, Protein G, a small single-chain with a 4-strand sheet and one helix.
- **1d66**, the Gal4 transcription factor DNA-binding domain complexed to DNA.

162-molecule, 27-unit cell "crystal":

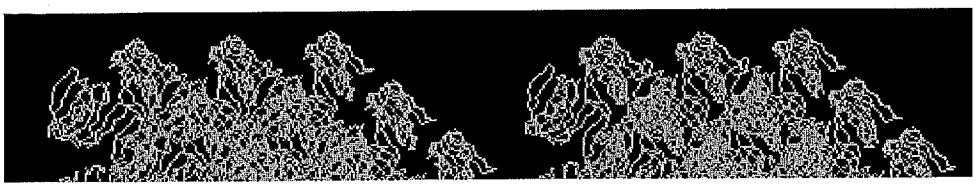
- **1pgb**, Protein G, alpha carbons only (9,072 atoms; with all non-hydrogen atoms, file contained 74,520 atoms). Model 1 contains the central asymmetric unit; model 2, the remainder of the central unit cell and 26 other unit cells. Each unit cell contains 6 copies of the one-chain molecule; this "crystal" contains 162 copies of the chain. To highlight the central asymmetric unit, in QuickViews, SELECT All, DISPLAY Spacefill. To display the unit cell, enter the command **set unitcell on** and change the background to black. Sorry, the unit cell is not centered, and I don't know how to fix that.

Gert Vriend of the Centre for Molecular and Biomolecular Informatics, Katholieke Universiteit Nijmegen, is working on a crystal contacts server, part of the WHAT IF WWW Interface. The present version can be found there under *Crystal Symmetry, Add shell of symmetry related residues*. However, it is not finished and the results are not guaranteed to be correct, nor is the resulting PDB file very compatible with Protein Explorer.

At present, the best way to view crystal contacts is to generate them with DeepView. This is a somewhat laborious process, despite the many timesaving features of this program. Here are instructions on how to generate crystal contacts with DeepView. In the resulting PDB file, it is difficult to visualize the contacts to the asymmetric unit because it is buried in the center of many chains. But from this file, a subset can be saved containing the asymmetric unit (or a single chain) plus only a shell of all contacting atoms within a specified distance, such as 5 Å (explained in the above instructions).



Above: Two views of crystal contacts for 1PGB, in Protein Explorer.
Below: Stereo view of "crystal" of 1PGB with central asymmetric unit in green.



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2. Dasgupta, S., G. H. Iyer, S. H. Bryant, C. E. Lawrence, and J. A. Bell. 1997. Extent and nature of contacts between protein molecules in crystal lattices and between subunits of protein oligomers. *Proteins.* **28:**494-514.
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Feedback to Eric Martz.